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Case Report

Dilated cardiomyopathy and sudden death in a teenager with palmar-plantar keratosis (occult Carvajal syndrome)

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Abstract

A 16-year-old female who was diagnosed with palmar-plantar keratosis and Papillon-Lefevre syndrome in life died following a period of stress/affray. Autopsy examination revealed evidence of minor trauma and a grossly abnormal heart. The heart was sent fresh and intact to a cardiac pathologist for examination. This revealed a dilated cardiomyopathy with left ventricular fibrosis, without fatty infiltration of the right ventricle. The features were in keeping with Carvajal syndrome, a variant of Naxos disease. This rare cardiac pathology and the interaction between stress (physiological, psychological and traumatic) and natural disease are discussed. The role of prompt referral for cardiac pathology assessment and association with the genodermatoses is also considered.

Keywords: Naxos disease; Carvajal syndrome; Sudden death; Traumatology; Cardiomyopathy

1. Introduction

Sudden death in adolescence is rare. If trauma and neoplasia are excluded, the autopsy investigation requires careful consideration. The following case centres on the interaction between natural disease and psychological/physical stress while illuminating a rare cardiac pathology.

1.1. Case report

This 16-year-old female was diagnosed with palmar-plantar keratoderma (PPK) and Papillon-Lefevre syndrome (PL) (periodontopathia) in life. PPK are a broad heterogeneous group of conditions associated with hyperkeratosis of the palms and soles due to mutations in the desmosomal cell adhesion proteins, plakoglobin and desmoplakin, which are widespread in the body, particularly epidermal tissue.[1–3] PL is an autosomal recessive disorder, associated with cathepsin-C gene mutations, resulting in characteristic dermatosis often with palmar hyperkeratosis and poor dentition.

In life extensive dental support was required as a consequence of significant dental caries, periodontitis, premature root resorption of primary teeth and hypodontia (with a total of 13 missing permanent teeth) (Fig. 1). In addition, desquamative gingivitis, angular chelitis, furrowed cobblestone oral mucosa and gingivae were encountered. Strict skin and dental care was required, but she otherwise led an active life with no other medical history. Tragically she was involved in an incident that involved verbal abuse with minor direct trauma. Immediately following this

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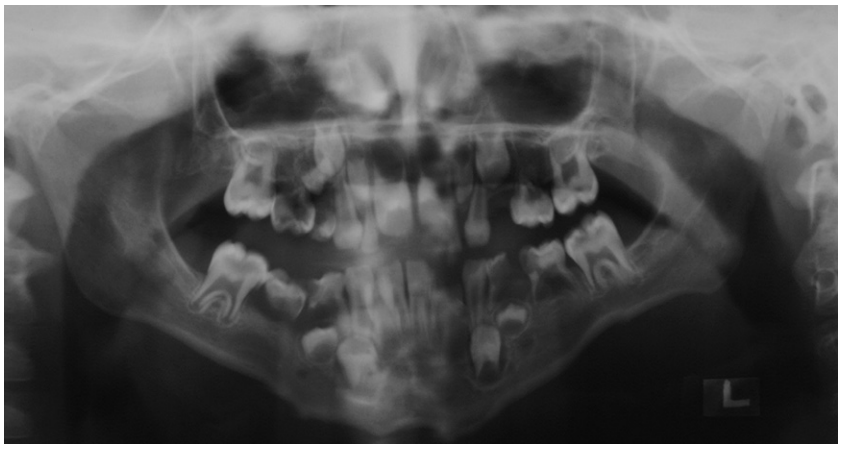

Fig. 1. Orthopantomograph taken at the age of six shows dental caries affecting primary and permanent dentition with abnormally advanced root resorption and periradicular pathology of the primary molars. In addition the patient was missing all wisdom teeth, second molars and second premolars and the UL 4 (13 teeth).

event, she ran approximately 100 m up an incline, and collapsed in fatal cardiac arrest.

An autopsy was performed a few hours after death. Minor bruising was identified externally. This comprised of an area of reddening under the right eye, 0.5 cm in diameter, a faint red bruise of the bridge of the nose, 0.8 cm diameter and a red bruise on the back of the right ear, 0.6×0.2 cm. The heart was found to be grossly abnormal. Other organs were normal apart from dental changes, woolly hair and keratotic skin. The heart was sent intact fresh to a cardiac pathologist for further investigation. The standard ancillary investigations of histology and toxicology were normal.

Cardiac examination identified normal external architecture with patchy fibrosis of the left ventricle epicardial free wall (Fig. 2). The coronary architecture and four

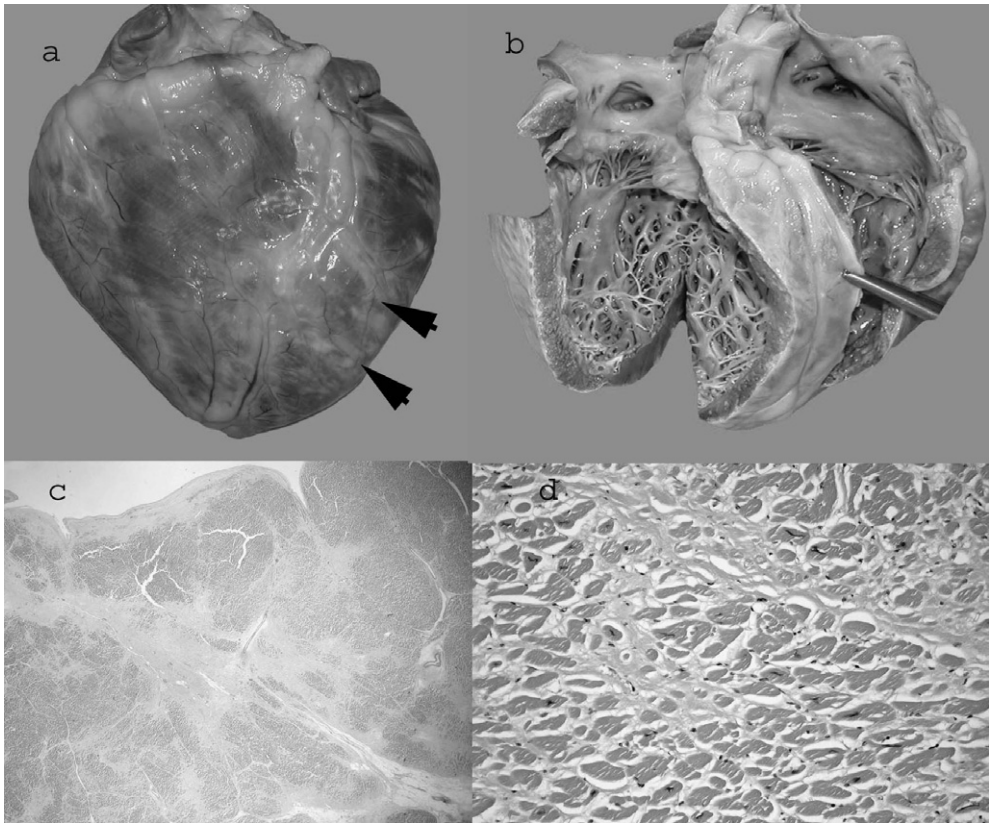

Fig. 2. Composite images. Macroscopic anterior view (a) showing areas subepicardial fibrosis, (b) dissected view showing left ventricle subendocardial fibrosis and dilated chamber, (c) left ventricle with fibrous scarring (H&E × 40), (d) left ventricle higher magnification (H&E × 200).

valves were within normal limits. There was mild biventricular dilatation with patchy left ventricular fibrosis macroscopically. At this point samples for electron microscopy, karyotype and DNA extraction were taken. Photography during dissection was procured.

Histology paralleled the macroscopic examination with left ventricle fibrosis. Myocyte loss was seen in a patchy distribution (Fig. 2). The genetic and ultrastructural investigations did not add further information. However, important negatives were noted, in that there was no myocarditis, atheroma, vasculitis, myocardial infiltration, myofibre disarray, fatty replacement or atypical infection. Overall, the abnormalities were of a dilated cardiomyopathy (DCM).

There was no other family history of DCM or sudden death. The skin abnormalities in association with DCM pointed to a diagnosis of Naxos disease, specifically its lesser variant Carvajal syndrome.

Naxos disease is a recessive PPK associated with woolly hair and arrhythmogenic right ventricular cardiomyopathy (ARVC).[1,4] Carvajal syndrome is associated with predominant left ventricular involvement.[1] Some have suggested that Naxos disease and Carvajal syndrome are the same disease with clinical and genetic heterogeneity.[1]

Following four teenagers were charged with manslaughter and affray. Three were convicted, but had their convictions for manslaughter overturned on appeal. The legal issues relating to this case have been discussed.[5]

2. Discussion

This case involves a probable case of Naxos disease, in the form of Carvajal syndrome. First described in Central America, this predominantly left sided cardiomyopathy describes a link with PPK.[1] Animal comparators exist.[1]

The patient fitted the clinical picture, external morphology and cardiac status, but did not have the more common associated cardiomyopathy: ARVC.[6,7] ARVC phenotype is characterised by fibro-fatty replacement of cardiomyocytes and extracellular matrix, predominately the right side, although left ventricle involvement can be seen.[3] Sampled tissue from the right ventricular infundibulum is particularly useful in such exclusion. ARVC predisposes to arrhythmia which may be precipitated by 'effort', although death at rest or during sleep is well-described.[1,4,8]

DCM is characterised by dilatation of the left ventricle, often with accompanying interstitial fibrosis.[9] Right ventricle involvement is less marked. In Carvajal syndrome, two phenotypes are seen: the first is characteristic DCM, whereas the second involves biventricular dilatation with a strong propensity for arrhythmia.[1] This pattern, known as Carvajal variant, is now considered a cardiomyopathy which could reflect an ARVC variation.[1] Clearly this permits an overlapping phenotype: classic Naxos disease and Carvajal syndrome.

Naxos disease, and its variants, show mutations in plakoglobin and desmoplakin.[1] These are important for cardiac myocytes coupling and electrical depolarisation to occur efficiently.[10] Problems in gap junction assembly are recognised to be associated with cardiac disease.[11] It is therefore likely that alongside cardiac tissues loss, as seen by patchy fibrosis, that altered cardiac conduction was likely to be present.

Other forms of differentials, including 'channelopathy', appear excluded by virtue of morphology.[12]

During any stressful event the 'Fight or Flight response' occurs under the influence of the central and sympathetic nervous systems. Catecholamine release from the adrenals is typically highest, not during activity, but about 3 min after cessation.[13] Catecholamine physiological effects are well-recognised, and may be detrimental, particularly if further stress compromised.[13–15] Potassium blood concentrations also increase during exercise/stress, but fall rapidly after cessation. The fall is such that hypokalemia may develop for as long as 90 min.[13] Both potassium concentration extremes are arrhythmogenic, although hyperkalemia is neutralised by the catecholamine release.[13] As such, once again, vulnerability appears to arise particularly after cessation. This phenomenon is known as ''post-exercise peril''.[13] It can be inferred that the stress of the abuse and assault, compounded by the sudden exertion in the escape run, conspired with the underlying cardiomyopathy and cardiac conduction pathology to cause an arrhythmic death. The role of the physical trauma identified in the precipitation of cardiac arrest is considered to be a minimal factor.

3. Conclusions

This case reports a rare cardiomyopathy (Naxos disease/Carvajal syndrome), presenting in association with a genetic dermatosis (PPK). Secondly, the risk of sudden natural death must be recognised and dermatopathologists, dermatologists and dental practitioners need an enhanced suspicion of associated cardiac pathology regarding PPK and PL syndromes. Thirdly when faced with sudden death of a young person, certain actions are required by the autopsy pathologist including detailed dissection of heart, coronary vessels and conduction system. Tissue preservation for genetic analysis, electron microscopy and possibly enzyme analysis should be considered. Photography and expert cardiac pathology opinion is advisable, particularly where criminal charges may be brought. Finally the interaction of natural disease arising with unnatural events needs consideration.

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References

1. Protonotarios N, Tsatsopoulou A. Naxos disease and carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Pathol* 2004;**13**:185–94.
2. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000;**9**:2761–6.
3. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000;**355**:2119–224.
4. Thiene G, Basso C, Calabrese F, Angelini A, Valente M. Twenty years of progress and beckoning frontiers in cardiovascular pathology: cardiomyopathies. *Cardiovasc Pathol* 2005;**14**:165–9.
5. Ormerod DC. Case comment R v Carey. *Crim Law Rev*:842–8.
6. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task force of the Working Group myocardial and pericardial disease of the European Society of cardiology and of the Scientific Council on cardiomyopathies of the International Society and Federation of cardiology. *Br Heart J* 1994;**71**:215–8.
7. Corrado D, Basso C, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: current diagnostic and management strategies. *Cardiol Rev* 2001;**9**:259–65.
8. Basso C, Thiene G. Adipositas cordis, fatty infiltration of the right ventricle, and arrhythmogenic right ventricular cardiomyopathy. Just a matter of fat? *Cardiovasc Pathol* 2005;**14**:37–41.
9. Gallo P, d'Amati G. Cardiomyopathy. In: Silver MS, Gotlieb AI, Schoen FJ, editors. *Cardiovascular pathology*. 3rd ed. New York: Churchill Livingstone; 2001. p. 285–325.
10. Severs NJ. The cardiac muscle cell. *Bioessays* 2000;**22**:188–99.
11. Severs NJ, Coppen SR, Dupont E, Yeh Hi, Ko YS, Matsushita T. Gap junction alterations in human cardiac disease. *Cardiovasc Res* 2004;**62**:368–77.
12. Towbin JA. Molecular basis for sudden cardiac death. *Cardiovasc Pathol* 2001;**10**:283–95.
13. DiMaio VJ, DiMaio D. Sudden death during or immediately after a violent struggle*Forensic pathology*. 2nd ed. Boca Raton: CRC Press; 2001. p. 499–506.
14. Goligorsky MS. The concept of cellular "fight-or-flight" reaction to stress. *Am J Physiol Renal Physiol* 2001;**280**:F551–61.
15. Qureshi EA, Merla V, Steinberg J, Rozanski A. Terrorism and the heart: implications for arrhythmogenesis and coronary artery disease. *Card Electrophysiol Rev* 2003;**7**:80–4.